Public Health Goal for Cadmium In Drinking Water

Prepared by

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February 1999

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We thank the U.S. EPA (Office of Water; Office of Prevention, Pesticides and Toxic Substances; National Center for Environmental Assessment) and the faculty members of the University of California with whom OEHHA contracted through the UC Office of the President for their peer reviews of the PHG documents, and gratefully acknowledge the comments received from all interested parties.

PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard

to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR CADMIUM IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.07 ppb has been developed for cadmium in drinking water to protect against nephrotoxicity from chronic exposure. This PHG is based on a LOAEL of 1 μg/kg bw, derived from an epidemiological study of a cross sectional sample of the adult Belgian population (Buchet et al., 1990). The health endpoint for this LOAEL was tubular damage indicated by the appearance in the urine of small proteins (retinol-binding protein, N-acetyl-β-glucosaminidase, and β_2-microglobulin) as well as aminoacids and calcium. The PHG was calculated using an overall uncertainty factor of 100 (made up of 10 for protection of sensitive individuals, 3 for extrapolation from LOAEL to NOAEL, and 3 for extrapolation from an adult population to the whole lifespan). A relative source contribution of 20% was used, based on the fact that the food contribution to exposure is often close to the maximum safe level.

When individuals are exposed to cadmium for many years, the metal gradually accumulates in their liver and kidneys. If the cadmium in the kidneys accumulates to a critical level of 50 μg/gram, then nephrotoxicity can result. Nephrotoxicity from cadmium first manifests itself by the appearance of small proteins and other chemicals in the urine. To ensure that cadmium levels in the kidney will not reach the critical level during the course of a lifetime, the intake of cadmium must be restricted. This forms the basis for the PHG.

Cadmium is a potential human carcinogen by the oral route. A carcinogenic potency was calculated based on induction of leukemia in zinc-deficient rats (Waalkes and Rehm, 1992). The drinking water level calculated in this way (0.09 ppb) was higher than the value calculated based on nephrotoxicity; therefore the value based on nephrotoxicity is the basis of the PHG.

INTRODUCTION

Cadmium enters drinking water mainly as an industrial pollutant. Individuals who consume cadmium in their drinking water over the course of many years are at risk for kidney disease owing to the toxic action of accumulated cadmium on the kidneys. To protect against this, a PHG of 0.07 ppb has been developed for cadmium in drinking water. The U.S. Environmental Protection Agency (U.S. EPA) has established a Maximum Contaminant Level (MCL) of 5 ppb for cadmium in drinking water. The California MCL is also 5 ppb.

CHEMICAL PROFILE

Chemical Identity

Cadmium is a metallic element with an atomic number of 48. It is a member of group IIB on the periodic table, along with zinc and mercury. Cadmium possesses two electrons in its outer electron shell. There are eight naturally occurring isotopes of cadmium, the most abundant of

which are ^{112}Cd and ^{114}Cd. Whereas none of the naturally occurring isotopes are radioactive, there are a number of radioactive artificial isotopes of cadmium (Weast et al., 1988).

Physical and Chemical Properties

Cadmium generally occurs in small quantities associated with other metals, particularly zinc. The atomic weight of cadmium is 112.41. Cadmium melts at 320.9°C, and boils at 767°C. The specific gravity of cadmium is 8.65. The most common valence is 2. Cadmium forms a number of salts. The most common cadmium salts are cadmium sulfate and cadmium sulfide. The latter is a yellow pigment (Hodgman, et al., 1961).

Production and Uses

Cadmium was discovered in 1817. It has a number of industrial and technological uses. It is used in alloys with low coefficients of friction and resistance to metal fatigue. It is also used in electroplating, and in barriers to control atomic fission in nuclear reactors. Production of cadmium in the United States was two to three million pounds annually during the 1980s (ATSDR, 1997). Production is expected to increase because of increased demand for NiCad batteries and other technological uses.

Sources

Almost all cadmium is obtained as a by-product in the treatment of zinc, copper and lead ores (Weast et al., 1988). The United States is a major producer of cadmium (ATSDR, 1997).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Humans are exposed to cadmium from all environmental media including air, drinking water, cigarette smoke, and food. Cigarette smoke and food are the major sources of exposure, with air and drinking water contributing lesser amounts (ATSDR, 1997).

Air

Ten million people in California are exposed to air concentrations of cadmium of 1 to 2.5 ng/m^3. The upper bound excess lifetime cancer risk for estimated atmospheric concentrations of cadmium in California has been estimated to be 30 cases per million people (CDHS, 1986).

Soil

Soil can become contaminated with cadmium from land disposal of cadmium wastes, from spreading of sewage sludge, and from the use of phosphate fertilizers (ATSDR, 1997). Despite all these potential sources, cadmium contamination of soil does not appear to be widespread (Bernard and Lauwery, 1984).

Water

Drinking water may become contaminated with cadmium due to its presence in solder used on metal pipes that carry drinking water. Cadmium in solder may be solubilized if the water is slightly acidic. It has been estimated that tap water typically contributes 2 to 4 µg per day to an individual's cadmium exposure (Hallenbeck, 1984).

Food

Food is the major source of exposure for nonsmoking adults (Bernard and Lauwerys, 1984). Adult exposure to cadmium via food has been estimated to range from 4 to 84 µg per day (Hallenbeck, 1984).

Cigarettes

Cigarettes are the most significant source of cadmium exposure to adults who smoke (Bernard and Lauwerys, 1984). Smokers are exposed to approximately 1.7 µg cadmium per cigarette (National Toxicology Program, 1991; ATSDR, 1997). Smoking a pack of cigarettes per day leads to an absorbed dose of approximately 1 to 3 µg cadmium per day (Nordberg et al, 1985; ATSDR, 1997).

METABOLISM AND PHARMACOKINETICS

Absorption

Absorption of cadmium in the gastrointestinal (GI) tract following ingestion has been extensively studied in animals and humans (Fox, 1983; ATSDR, 1991, 1997). McLellan et al. (1978) used total body counting of radioactively labeled cadmium to determine absorption in 14 healthy subjects. Radioactively labeled chromium was used to determine the point of complete elimination of unabsorbed cadmium from the GI tract. For the 14 subjects, the average body retention of cadmium determined between seven and fourteen days after the disappearance of the chromium marker from the body was 4.6% with a standard deviation of 4%, and a range of 0.7% to 15.6% (McLellan et al., 1978). The study on which the PHG is based (Buchet et al., 1990) used oral absorption of 5% as part of a biokinetic model to estimate the body burden from urinary cadmium levels in human subjects.

Distribution

Cadmium ingested by humans is distributed throughout the body, but accumulates mainly in the liver and kidneys (Fox, 1983; ATSDR, 1991, 1997). Cadmium has a biological half-life in the human kidney of two to three decades (Fox, 1983; ATSDR, 1991, 1997).

Metabolism

There is no evidence that cadmium undergoes any direct metabolism such as oxidation or reduction in biological systems. However, the positively-charged Cd^{2+} ion does bind to negatively-charged groups in macromolecules, such as sulfhydryl groups in proteins (ATSDR, 1997).

Cadmium in animal and human tissue is bound primarily to metallothionein (Fox, 1983; ATSDR, 1991, 1997). Cadmium circulates in the blood plasma bound to metallothionein, albumin and possibly other molecules (ATSDR, 1997).

As many as seven cadmium ions can bind to a single molecule of metallothionein (ATSDR, 1997). Binding to metallothionein protects the liver and kidneys from the toxic effects of cadmium (ATSDR, 1997). When the total amount of cadmium in the kidney reaches a critical level (approximately 200 µg/gram) the cadmium begins to damage the kidney, either because not all the cadmium can remain bound to metallothionein, or because even metallothionein-bound cadmium can be toxic at these concentrations (Suzuki and Cherian, 1987; ATSDR, 1997).

Excretion

Cadmium excretion rates can vary over a wide range. After reviewing the literature, Kjellstrom and Nordberg (1985) developed a range of half-times from their kinetic model of the human kidney of between 6 and 38 years.

The study on which the PHG is based (Buchet et al., 1990) used an excretion rate of 0.005% of body burden, based on the work of Friberg et al. (1985). Friberg et al. reviewed a number of human studies of cadmium excretion, and reported 0.005% as a representative value to be used in modeling of cadmium kinetics.

Physiological/Nutritional Role

Cadmium is not an essential element, and is not known to have any physiological role in the body.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Acute oral LD_{50}s for rats and mice range from approximately 100 to 300 mg/kg (ATSDR, 1991, 1997; Shimizu and Morita, 1990). Very young animals have lower LD_{50}s than adult animals, possibly due to greater absorption of ingested cadmium in the younger animals (ATSDR, 1991, 1997).

Subchronic and Chronic Toxicity

Cardiovascular Toxicity

Rats chronically exposed to cadmium in drinking water at levels of 0.1 to 20 parts per million (ppm) have elevated systolic and diastolic blood pressure, as well as higher mortality resulting from blood pressure effects (Ohanian and Iwai, 1979; Perry, Erlanger and Perry, 1980; Kopp et al., 1982). The lowest level at which these hypertensive effects were observed in rats (0.1 ppm) is ten times the current California Maximum Contaminant Level (MCL), which is 10 parts per billion (10 ppb). The hypertensive effects of cadmium were reduced when selenium, zinc or copper was added to drinking water (Perry, Erlanger and Perry, 1980).

Long-term (9 years) exposure of Rhesus monkeys to 100 ppm cadmium in the diet led to increased blood pressure in the first 1.5 years relative to controls, and inhibited the hypertension seen in aging controls (Akahori, et al., 1994).

Renal Toxicity

Studies in rats, mice and rabbits demonstrate that oral exposure to cadmium leads to renal damage (ATSDR, 1997). Histopathological effects, including focal necrosis of proximal tubular epithelial cells and cloudy swelling in renal tubules have been observed in rats following oral exposure to cadmium (Cha, 1987). Animal studies confirm the finding in humans that a critical level in the kidneys leads to proteinuria (Shaikh et al., 1989; ATSDR, 1997).

Genetic Toxicity

Positive results have been obtained in some bacterial mutagenicity tests, and in most mutagenicity tests in mammalian cells (ATSDR, 1997). Chromosomal aberrations were significantly increased in most studies involving treatment of mammalian cells in culture (ATSDR, 1997).

There was no evidence of germ cell mutations (dominant lethal mutations) in male rats exposed to cadmium in drinking water for 70 days at doses up to 68.8 ppm (Zenick et al., 1982). In general cadmium appears to have the capacity to cause mutations and chromosomal aberrations, but is not an effective mutagen or clastogen by the oral route (ATSDR, 1997).

Developmental and Reproductive Toxicity

A number of studies in rats and mice indicate that oral exposure of pregnant females during gestation can result in fetotoxicity, usually in the form of reduced fetal or pup weights (Sorell and Graziano, 1990; ATSDR, 1991, 1997). Malformations, primarily of the skeleton, have been found in some rodent studies (Baranski, 1985; ATSDR, 1991, 1997). Female rats orally exposed to cadmium at a dose of 0.7 mg/kg/day prior to gestation (Baranski et al., 1983) or to a dose of 0.7 mg/kg/day during gestation (Ali et al., 1986) produced offspring with impaired neurobehavioral development (reduced exploratory locomotor activity, and decreased

performance on the "rotarod" test). This endpoint appears to be the most sensitive indicator for developmental toxicity of cadmium by the oral route in animals (ATSDR, 1991, 1997).

Oral exposure to cadmium for ten days caused testicular atrophy and necrosis in rats and mice, but only at near-fatal doses (Borzelleca et al., 1989; ATSDR, 1991, 1997).

A study by Laskey et al. (1980) provides a NOEL for male reproductive toxicity due to chronic exposure to cadmium in drinking water. The study involved exposure of male and female rats to cadmium chloride in drinking water, from the beginning of gestation, through postnatal growth and maturation and one round of mating of the F_1 generation. Cadmium concentrations in the drinking water were 0, 0.1, 1.0, and 5.0 ppm. While females as well as males were exposed, the LOEL of 5.0 ppm was based on reduced epididymal sperm counts – an endpoint for which only the males' exposure is relevant. The NOEL for this endpoint was 1.0 ppm.

Immunotoxicity

Studies in rats, mice and monkeys have demonstrated that oral exposure of these animals to cadmium can lead to complex effects on the immune system (ATSDR, 1991, 1997; Descotes, J., 1992). Oral exposure of rats to cadmium in drinking water for 30 days at 200 and 400 ppm led to altered natural killer (NK) cell activity (Cifone, et al., 1989). NK cell activity was decreased relative to controls during the first 30 days of treatment, and increased relative to controls after 30 days. Total duration of the experiment was "almost six months" (Cifone, et al., 1989). The LOAEL for this NK cell effect was 28 mg/kg/day (Cifone, et al., 1989; ATSDR, 1991, 1997). Peripheral blood lymphocytes were also increased throughout the experiment (Cifone, et al., 1989).

Blakley (1986) treated 41 female albino Swiss mice with cadmium in drinking water at doses of 0, 10 and 50 ppm for 280 days. Spontaneous virally-induced lymphocytic leukemia was observed in all treatment groups. Deaths from lymphocytic leukemia were increased 33% (from 18 to 24) in the two cadmium exposed groups ($p=0.02$). This experiment indicates that cadmium exposure enhances viral-induced tumor production (Blakley, 1986).

Investigators administered 50 ppm cadmium in drinking water to young male mice for three weeks (Borgman, et al., 1986). After cessation of treatment there was a suppression in the number of splenic plaque-forming cells in response to sheep red blood cell immunization. The treated mice also showed a decrease in the number of circulating lymphocytes (Borgman, et al., 1986). Thomas et al. (1985) treated adult female $B6C3F_1$ mice with distilled water containing 10, 50 or 250 ppm cadmium. They observed a dose-related increased susceptibility to Herpes simplex type 2 virus, and an increase in macrophage phagocytosis following cadmium treatment (Thomas et al., 1985). Other mouse experiments with effects on immunological functions are reviewed and discussed by ATSDR (1992).

Orally administered cadmium at a dose of 5 mg/kg body weight increased the cell-mediated immune response of Rhesus monkeys (Chopra et al., 1984). Calcium deficiency interferes with this effect (Chopra et al., 1984). A review of the animal data indicates that orally administered cadmium has complex effects on the immune system (ATSDR, 1991, 1997).

Neurotoxicity

Neurological effects were reported in rats chronically exposed to cadmium by the oral route in six studies (ATSDR, 1997). The lowest observed adverse effect level (LOAEL) for neurological effects, decreased motor activity in rats, is 50 mg/kg-day (Kotsonis and Klaasen, 1977; ATSDR, 1997).

Carcinogenicity

Rats exposed to cadmium chloride by subcutaneous injection showed a dose-dependent increase in the incidence of injection site tumors, testicular tumors and prostate tumors (Waalkes et al., 1988; Waalkes et al., 1991). It appears clear that, in order for cadmium to cause these tumors at remote sites, the cadmium must have entered the bloodstream and been transported to the site. Exposure resulting in blood absorption is referred to as "systemic" exposure. These results suggest that if cadmium enters the bloodstream following oral exposure in humans it would be carcinogenic. Although there is much evidence in the literature that suggests that oral cadmium is not carcinogenic in humans (Collins et al., 1992), recent evidence from epidemiological studies and rat diet studies indicate that it may have carcinogenic effects by the oral route (Waalkes and Rehm, 1992; Collins et al., 1996).

A study by Waalkes and Rehm (1992) examined the effect of dietary cadmium on male Wistar rats. Rats were exposed to cadmium in the diet at levels of 0, 25, 50, 100 and 200 ppm. One group of rats was given a diet with adequate zinc (60 ppm zinc), and another group was given a zinc-deficient diet (7 ppm zinc). This was to study the effect of zinc on the induction of tumors by cadmium. Cadmium is believed to exert toxic effects by interfering with metabolic processes that involve zinc (Waalkes and Rehm, 1992; Collins et al., 1996). The incidence of "prostatic proliferative lesions," including both hyperplastic lesions and adenomas of the prostate, was increased over controls (0 ppm cadmium) in both the zinc-adequate and zinc-deficient rats fed 50 ppm cadmium. Cadmium treatment also resulted in an elevated leukemia incidence in both zinc-adequate and zinc-deficient rats (Waalkes and Rehm, 1992). This study indicates that oral cadmium exposure is associated with tumors of the prostate, testes, and hematopoietic system in rats (Waalkes and Rehm, 1992). Cadmium should therefore be regarded as a potential human carcinogen by the oral route (Vainio, et al., 1994; Collins et al., 1996). In addition to the Waalkes and Rehm study, a review of recent epidemiological evidence by IARC (1993) concluded, primarily on the evidence of lung cancer in humans exposed to cadmium, that "there is sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds." (IARC, 1993, quoted in Collins et al., 1996).

Toxicological Effects in Humans

Acute Toxicity

In cases where oral ingestion of cadmium has been used as a means of committing suicide, death has resulted from massive fluid loss, edema, and widespread organ destruction (ATSDR, 1991, 1997, Buckler et al., 1986). The doses ingested in two such cases were estimated at 25 mg/kg (Wisniewska-Knypl et al., 1971) and 1,500 mg/kg (Buckler et al., 1986).

Acute effects of cadmium poisoning include vomiting, diarrhea and other acute gastrointestinal effects (ATSDR, 1991, 1997). These are similar to the acute effects of lead poisoning. The effects have been observed in children drinking soft drinks with 16 mg/L of cadmium (ATSDR, 1991, 1997).

Chronic Toxicity

Cardiovascular Toxicity

Evidence for an effect of cadmium on blood pressure and mortality in humans is based on analysis of tissue samples taken from individuals who died from the complications of high blood pressure. Epidemiological studies have shown that these individuals had higher kidney cadmium concentrations (36 μg/g wet weight) than individuals who died from unrelated causes (27 μg/g wet weight)(Lener and Bibr, 1971; Schroeder, 1965). The difference between the hypertensive individuals and controls was statistically significant ($p<0.05$). However, other studies have not confirmed these findings (Syversen et al., 1976). One cause of discrepancies in this area may be that smoking increases both hypertension and renal cadmium levels. Increased occurrence of hypertension increases the population risk of mortality by increasing the frequency of strokes and other cardiovascular catastrophes (Schwartz et al., 1985).

Renal Toxicity

Long-term exposure to cadmium at doses of approximately 140 μg/day results in critical damage to the kidney, particularly the proximal tubules (Friberg et al., 1974; Friberg, 1984; Nogawa, et al., 1989; ATSDR, 1991, 1997). Even in its early stages, this kidney damage appears to be an irreversible health effect (Hutton, 1987). The earliest indication of kidney damage is the presence of low molecular weight proteins (alpha, beta, and gamma globulins) in the urine. These appear in the urine because of failure to reabsorb them in the proximal tubules. Later consequences of kidney damage are aminoaciduria, phosphaturia, and glucosuria (Friberg et al, 1974; Friberg, 1984). This type of kidney damage occurs in workers who have blood cadmium levels above 1 μg/dL of blood (Buchet et al., 1980).

Later, Buchet et al. (1990) avoided the healthy worker effect by performing a cross-sectional study on 1699 Belgian subjects between the ages of 20 and 80 years. This study was undertaken to determine whether environmental exposures (by all routes) were associated with renal dysfunction, using the urinary excretion of retinol-binding protein, N-acetyl-β-glucosaminidase, β_2-microglobulin, aminoacids, and calcium as markers of renal tubular dysfunction. Cadmium

body burden of the subjects was estimated from the urinary levels of cadmium, based on a biokinetic model. The investigators found a positive relationship between cadmium body burden and renal tubular dysfunction. The LOAEL for this effect was 1 μg/kg body weight, associated with a critical level of 50 μg/g kidney wet weight (Buchet et al., 1990).

Genetic Toxicity

In an area of China with cadmium-polluted drinking water, individuals with higher levels of cadmium in their urine (>3 μg/L) had more frequent chromosomal aberrations (and more severe aberrations) in their peripheral lymphocytes than individuals with lower cadmium in their urine (<3 μg/L) (Tang, et al., 1990).

Developmental and Reproductive Toxicity

Developmental and reproductive effects of cadmium were reviewed by OEHHA (OEHHA, 1996). The review concluded that the overall evidence from human studies of elevated cadmium levels in humans and adverse reproductive effects, including pre-term labor and low birth weight for gestational age, is consistent with that from experimental animals (OEHHA, 1996).

Immunotoxicity

There are almost no data on the effects of oral exposure to cadmium on the human immune system (ATSDR, 1991, 1997). A study by Yamada et al. (1989) indicates that both human T and B peripheral lymphocytes are able to produce metallothioneins in response to cadmium exposure, suggesting that both cell types have a mechanism of protection against cadmium cytotoxicity. A study of workers exposed to lead and cadmium by inhalation showed that the two metals have opposite effects on gamma-interferon levels (Yucesoy et al., 1997). Whereas lead exposure caused a reduction in gamma-interferon levels, workers exposed to cadmium showed significantly enhanced levels of gamma-interferon (Yucesoy et al., 1997).

Neurotoxicity

Epidemiological studies of humans with environmental cadmium exposure have indicated effects on verbal Intelligence Quotient (IQ) and disruptive behavior, but these studies are subject to poor quantitation of cadmium exposure and confounding by lead exposures (ATSDR, 1991, 1997).

Skeletal Toxicity

Tubular degeneration of the kidneys leads to loss of calcium which in turn leads to bone disease (Friberg et al, 1974; Friberg, 1984). This syndrome appears in its extreme form in areas of Japan where rice is contaminated with cadmium because of nonferrous metal mining activities. In Japan, the effect of cadmium on bone structure, which affects mostly post-menopausal women, is known as “itai-itai disease,” which means “ouch-ouch disease,” in reference to the painfulness of this chronic condition (Friberg et al., 1974).

Carcinogenicity

Cadmium exposure via inhalation has led to an increased frequency of lung cancer in battery workers (Friberg, 1984). Prostate cancer may also be increased by this exposure (Friberg, 1984). Cadmium has been shown to be carcinogenic in humans by the inhalation route of exposure (Elinder et al., 1985; IARC, 1993; Collins et al., 1996). Cadmium is regarded as a potential human carcinogen by the oral route because: 1) it is carcinogenic in humans by inhalation, 2) it is genotoxic in *in vitro* systems, including human cells, and 3) it has induced tumors in rats exposed via diet (IARC, 1993; Collins et al., 1996).

Humans exposed to cadmium by inhalation developed lung cancer and prostate cancer (Elinder et al., 1985; Ades and Kazantzis, 1988; ATSDR, 1991, 1997). Both of these cancer types have been verified in rodents exposed to cadmium aerosols (Oldiges et al., 1989; ATSDR, 1991, 1997).

An environmental epidemiological study conducted in Alberta, Canada (Bako, et al., 1982) showed that elevated rates of prostate cancer were geographically related to elevated levels of cadmium in drinking water, soil or crops. However, in this and similar studies, no attempt was made to quantitate the exposure of the populations to cadmium (ATSDR, 1997).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Kidney damage appears to depend on the renal concentration of cadmium reaching a critical level which is generally accepted to be 200 µg/gram, wet weight (Friberg et al., 1974). According to epidemiological studies reported from Japan, the critical level may actually be 120 to 150 µg/gram (Nogawa et al., 1986). However, the higher value, 200 µg/gram, is still generally accepted (IRIS, 1998).

Metallothionein (MT) is a protein which binds not only cadmium, but also zinc, copper, mercury, silver, and tin (Hallenbeck, 1984). The binding of cadmium to MT protects against kidney damage when the cadmium concentration in the kidney cortex is below the critical level. If the concentration of cadmium in the kidney exceeds the capacity of the kidney to synthesize MT and bind cadmium, then the excess cadmium will remain unbound. Unbound cadmium damages the kidney tubules. Friberg estimated that a daily intake of 350 µg of cadmium for 50 years would lead to the 200 µg/gram "critical level" assuming 4.5% absorption and 0.01% excretion (Friberg et al., 1974). The World Health Organization (WHO) set a Provisional Tolerable Daily Intake (PTDI) of 60 to 70 µg of cadmium per day based on the 200 µg/gram critical level (WHO, 1984). This is a daily intake estimated to result, by age 50, in a concentration of cadmium in the kidney cortex which is one fourth of the critical level (WHO, 1984).

In a study based on a large sample (n=1699) of the general population, Buchet et al. (1990) found that the critical level in the kidney was 50 µg/g wet weight. This level was associated with a LOAEL of 1 µg/kg body weight, the intake rate that would produce this critical level over 50

years. This study was based on subjects aged 20 to 80 years. This LOAEL does not take into account the possibility that the rate of accumulation of cadmium in the kidneys may be different for children.

Carcinogenic Effects

The best available study for the quantitation of the carcinogenic potency of cadmium is the rat study by Waalkes and Rehm (1992) described above. This study found an increase in the incidence of prostate tumors and leukemia in rats exposed to cadmium in the diet. The best data set for calculating a cancer potency is the data on leukemia induction in the zinc-deficient rats. This data set is preferred because leukemia is a clearly neoplastic endpoint that is related to a significant cancer in humans. This data set also exhibits a much clearer dose/response curve than the prostate tumor data. The dataset from the zinc-deficient rats is chosen because there was a higher incidence of leukemia in these rats, yielding a more definite dose/response.

The data from the Waalkes and Rehm study is given in the following table.

Group	Rats at Risk	Dietary Zinc Level (ppm)	Cadmium dose (ppm)	Number of Rats with Leukemia
1 (control)	27	7	0	2
2	26	7	25	1
3	26	7	50	3
4	25	7	100	5
5	25	7	200	7

These data were used to calculate a q_1* and cancer slope factor (CSF) using ToxRisk version 3. The calculation was done using standard defaults, including (body weight)$^{3/4}$ extrapolation from rats to humans. The values obtained were as follows.

Q_1* = 0.44 (mg/kg-day)$^{-1}$

CSF = 0.38 (mg/kg-day)$^{-1}$

The CSF is the preferred value for calculating a public health goal for drinking water.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for cadmium in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL/LOAEL	=	No-observed-adverse-effect-level or lowest-observed-adverse-effect-level
BW	=	Adult body weight (a default of 70 kg for male or 60 kg for female)
RSC	=	Relative source contribution (a default of 20% to 80%)
UF	=	Uncertainty factors (typical defaults of a 10 to account for inter-species extrapolation, a 10 for uncertainty from the subchronic duration of the principal study, a 10 for potentially sensitive human subpopulations, and a 10 for extrapolating from LOAEL to NOAEL.)
L/day	=	Adult daily water consumption rate (a default of 2 L/day)

Friberg et al. (1985) reported a LOAEL for cadmium of 140 µg/day based on an epidemiological study of kidney effects in workers.

Food contributes a great deal of cadmium exposure, therefore the relative source contribution for drinking water should be at the low end of the range (20%). An uncertainty factor of 10 will be used to protect sensitive individuals, and another 10 for extrapolating from a LOAEL to a NOAEL, for a total UF of 100.

$$C = \frac{140\ \mu g/day \times 0.2}{100 \times 2\ L/day} = 0.14\ \mu g/L, \text{ or } 0.14\ ppb$$

A later study (Buchet et al., 1990) determined the LOAEL to be 1 µg/kg body weight. This study relies on data from the "general population" thereby eliminating the "healthy worker effect." If we use this LOAEL, and assume an adult body weight of 70 kg, the calculation becomes

$$C = \frac{1\ \mu g/kg\text{-}day \times 70\ kg \times 0.2}{100 \times 2\ L/day} = 0.07\ \mu g/L, \text{ or } 0.07\ ppb$$

The uncertainty factor here is made up of 10 for protection of sensitive individuals (such as smokers and diabetics), 3 for extrapolating from a LOAEL to a NOAEL, and 3 for uncertainty in applying adult biokinetics to the entire age range from infancy to adulthood. In combining these factors, the 3 is regarded as the square root of 10. An uncertainty factor of 3 (rather than the usual default of 10) is used for extrapolating from a LOAEL to a NOAEL, because the LOAEL is based on minimal effects in 10% of nonsmokers. The LOAEL is probably very close to being a NOAEL. A factor of 3 is used to account for uncertainty about the biokinetics of the childhood portion of the life span of the studied individuals, because the adults who were studied were probably exposed to similar levels of cadmium as children, so the LOAEL is probably applicable to individuals exposed both as children and adults.

The Buchet (1990) study is the best study on which to base the PHG, since it is based on data from the general population (rather than workers). Therefore, a PHG of 0.07 μg/L or 0.07 ppb has been developed for cadmium in drinking water.

Carcinogenic Effects

The cancer slope factor (CSF) for cadmium based on leukemia in zinc-deficient rats (Waalkes and Rehm, 1992) is 0.38 $(mg/kg\text{-}day)^{-1}$.

This can be used to calculate a drinking water according to the following equation.

$$C = \frac{bw \times \text{cancer risk}}{CSF \times WI}$$

Where bw is adult body weight (70 kg), and WI is water intake (2 L/day).

$$C = \frac{70\ kg \times 1\times10^{-6}}{[0.38\ (mg/kg\text{-}day)^{-1}]\times 2\ L/day} = 9.2\times10^{-5}\ mg/L = 0.092\ \mu g/L \text{ or } 0.092\ ppb$$

This can be rounded off to 0.09 ppb. This is higher than the value calculated above for non-carcinogenic (nephrotoxic) effects. Therefore, the PHG is 0.07 ppb, based on nephrotoxicity.

RISK CHARACTERIZATION

The sources of uncertainty in the calculation of the PHG for cadmium are as follows:

Endpoint: The noncarcinogenic endpoint chosen was nephrotoxicity. Reproductive toxicity is also an endpoint for cadmium. The study by Laskey et al. (1980) of the effect of cadmium in drinking water on male reproductive toxicity reported a NOEL of 1 ppm. If this endpoint were used as the basis for the PHG, the value would be 2 ppb, based on an uncertainty factor of 100, made up of 10 for interspecies extrapolation, and 10 for protection of sensitive individuals, and a RSC of 20%. This is significantly higher than the value calculated using the nephrotoxicity endpoint.

LOAEL: The exact level of cadmium in the kidney that causes toxicity is not known with certainty. A number of published reports arrive at different "critical levels." The study on which the PHG is based (Buchet et al., 1990) used a biokinetic model to estimate body burden and kidney concentration based on urinary cadmium levels in human subjects. The biokinetic model was based on estimates of absorption and excretion rats from earlier studies by Friberg et al. (1985). Both the model itself and the parameters in it are a source of uncertainty in estimating the critical level.

RSC: The relative source contribution depends on the amount of cadmium exposure contributed by other sources of cadmium, notably diet and cigarette smoking. Cigarettes are the main source of cadmium for smokers. Diet is the main source for nonsmokers.

UF: The usual uncertainty factor of 10 has been used to protect sensitive individuals. There is uncertainty as to how much variation in sensitivity to cadmium may exist between different individuals. Diabetics and smokers may be more sensitive to cadmium than the general population, but it is not known how much more sensitive they may be. An additional uncertainty factor of 3 has been used to extrapolate from a LOAEL to a NOAEL. The true NOAEL for this effect has not been determined directly from experimental data. The childhood portion of the cadmium accumulation in the body was not dealt with separately in the biokinetic model. This is a separate source of uncertainty for which an uncertainty factor of 3 was used.

Water Consumption: The estimated water consumption for adults is two liters per day. The actual amount of water consumed by adults varies depending on their size and weight, weather conditions, diet and other factors.

All of the above factors contribute to the uncertainty of this calculation. The PHG is a reasonable estimate of a level for cadmium in drinking water which is not expected to result in nephrotoxicity or any other toxic effect assuming the water is consumed over a lifetime.

OTHER REGULATORY STANDARDS

The U.S. EPA MCL for cadmium is 5 μg/L. U.S. EPA established a reference dose (RfD) for drinking water of 0.5 μg/kg-day (IRIS, 1998). This RfD is based on a no-observed-adverse-effect-level (NOAEL) of 200 μg/gram in the renal cortex (Friberg et al., 1985; IRIS, 1998). The RfD incorporates a 10-fold uncertainty factor for protection of sensitive populations.

Cadmium is listed by the California Air Resources Board as a toxic air contaminant (TAC) (California Administrative Code, Title 17, Section 93000). Data on cadmium emissions must be included in monitoring programs under the air toxics hot spots program. Levels of cadmium in California air are regulated to limit cancer risk.

The threshold limit value (TLV) for cadmium dust and salts as cadmium is 0.05 mg/m^3 as a time-weighted average. This level was set to prevent proteinuria, pulmonary edema and emphysema. There is a proposal by the TLV Committee of the American Conference of Government and Industrial Hygienists to lower the TLV to 0.01 mg/m^3 to protect against kidney damage and lung cancer (ACGIH, 1996).

According to section 66699 of the California Health and Safety Code, Title 22, a waste will be classified as a hazardous waste if the soluble threshold limit concentration (STLC) of cadmium exceeds 1.0 μg/ml, or the total threshold limit concentration (TTLC) of cadmium exceeds 100 mg/kg (California Health and Safety Code, section 66699).

There are no standards or action levels for cadmium in individual foods, however, a WHO Committee on Food Additives recommended a provisional maximum tolerable weekly cadmium intake of 400 to 500 µg cadmium from all sources (WHO, 1972). This is equivalent to 60 to 70 µg/day. Adult exposure to cadmium via food has been estimated to range from 4 to 84 µg/day (Hallenbeck, 1984).

The International Agency for Research on Cancer (IARC, 1993) classifies cadmium as a Group 1 carcinogen -- a known human carcinogen. U.S. EPA has classified cadmium as a probable human carcinogen by inhalation (Group B1) based on animal and human data (IRIS, 1998). The 10^{-6} cancer risk for cadmium calculated by U.S. EPA corresponds to an exposure of 12 nanograms per day. Under the California Toxic Air Contaminant Program, the 10^{-6} cancer risk was taken to be an inhaled dose of 1.7 ng/day (CDHS, 1986; Collins et al., 1992). Cadmium is not considered to be a carcinogen by the oral route (see above).

In accordance with the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), "cadmium and cadmium compounds" are listed (since October 1, 1987) on the Proposition 65 list as carcinogens (OEHHA, 1998). Cadmium is also listed (since May 1, 1997) as a developmental toxicant, and as a male reproductive toxicant (OEHHA, 1998). The level of cadmium exposure that poses no significant risk of cancer for purposes of Proposition 65 is 0.05 µg per day by inhalation (Title 22, California Code of Regulations (CCR), Section 12705(b)). Ingestion of cadmium poses no significant risk of cancer for purposes of Proposition 65 so long as the exposure does not exceed any State or Federal standards for ingested cadmium.

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